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L3: Entry 11 of 81

File: USPT

Dec 18, 2001

US-PAT-NO: 6331303

DOCUMENT-IDENTIFIER: US 6331303 B1

TITLE: LKTA deletion mutant of P. haemolytica

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME

CITY

STATE

ZIP CODE

COUNTRY

Briggs; Robert E.

Boone

IA

Tatum; Fred M.

Ames

IA

ASSIGNEE-INFORMATION:

NAME

CITY STATE ZIP CODE COUNTRY TYPE CODE

Biotechnology Research and Development
Corporation

Peoria IL

02

APPL-NO: 09/ 160340 [PALM]

DATE FILED: September 25, 1998

PARENT-CASE:

This application claims the benefit of co-pending provisional application Ser. No. 60/060,060, filed Sep. 25, 1997, which is incorporated by reference herein.

INT-CL: [07] A61 K 39/102

US-CL-ISSUED: 424/255.1; 424/234.1, 435/172.1, 435/252.3, 435/69.1

US-CL-CURRENT: 424/255.1; 424/234.1, 435/252.3, 435/471, 435/69.1

FIELD-OF-SEARCH: 424/234.1, 424/255.1, 536/23.7, 435/320.1, 435/69.1, 435/243, 435/252.3, 435/172.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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PAT-NO

ISSUE-DATE

PATENTEE-NAME

US-CL

5422110

June 1995

Potter et al.

5733780

March 1998

Briggs et al.

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO97 16531	May 1997	WO	
97/41823 A	November 1997	WO	

OTHER PUBLICATIONS

- George L. Murphy et al. "Hemolytic Activity of the Pasteurella haemolytica Leukotoxin" Infection and Immunity, Aug. 1995, pp. 3209-3212.
- Natalie D. Fedorova & Sarah K. Highlander "Generation of Targeted Nonpolar Gene Insertions and Operon Fusions in Pasteurella haemolytica and Creation of a Strain that Produces and Secretes Inactive Leukotoxin" Infection and Immunity, Jul. 1997, pp. 2593-2598.
- Fred M. Tatum et al. "Construction of an isogenic leukotoxin deletion mutant of Pasteurella haemolytica serotype 1: characterization and virulence" Microbial Pathogenesis 1998; 24:37-46.
- Robert E. Briggs et al. "Development and testing of a unique strain of Pasteurella haemolytica for use in studies on colonization of the respiratory tract of cattle" AJVR, vol. 59, No. 4, Apr. 1998.
- Robert E. Briggs et al. "Rapid spread of a unique strain of Pasteurella haemolytica serotype 1 among transported calves" AJVR, vol. 59, No. 4, Apr. 1998.
- Glynn H. Frank et al. "Colonization of the tonsils and nasopharynx of calves by a rifampicin-resistant Pasteurella haemolytica and its inhibition by vaccination" Am J Vet Res., vol. 56, No. 7, Jul. 1995.
- G.H. Frank et al. "Serotype-specific inhibition of colonization of the tonsils and nasopharynx of calves after Pasteurella haemolytica serotype A1 after vaccination with the organism" Am J Vet Res, vol. 55, No. 8, Aug. 1994.
- G.H. Frank & R.E. Briggs "Colonization of the tonsils of calves with Pasteurella haemolytica" Am J Vet Res, vol. 53, No. 4, Apr. 1992.
- Glynn H. Frank "Infection of the middle nasal meatus of calves with Pasteurella haemolytica serotype 1" Am J Vet Res, vol. 50, No. 8, Aug. 1989.
- David C. Straus et al. "In Vivo Production of Neuraminidase by Pasteurella haemolytica in Market Stressed Cattle After Natural Infection" Current Microbiology, vol. 37 (1998) pp. 240-244.
- Glynn H. Frank et al. "Respiratory tract disease and mucosal colonization by Pasteurella haemolytica in transported cattle" AJVR, vol. 57, No. 9, Sep. 1996 pp. 1317-1320.
- Homchampa et al. "Cross protective immunity conferred by a marker-free aro A mutant of Pasteurella multocida" Vaccine 1997 vol. 15, No. 2.
- Beaumont et al. "Identification and Characterization of alcR, a Gene Encoding an AraC-Like Regulator of Alcaligin Siderophore Biosynthesis and Transport in Bordetella pertussis and Bordetella bronchiseptica" Journal of Bacteriology, Feb. 1998, pp. 862-870, vol. 180, No. 4.
- Link et al. "Methods for Generating Precise Deletions and Insertions in the Genome of Wild-Type Escherichia coli: Application to Open Reading Frame Characterization" Journal of Bacteriology, Oct. 1997, pp. 628-6237, vol. 179, No. 20.
- Cotter and Miller "BvgAS-Mediated Signal Transduction: Analysis of Phase-Locked Regulatory Mutants of Bordetella bronchiseptica in a Rabbit Model" Infection and Immunity Aug. 1994, pp. 3381-3390, vol. 62, No. 8.
- Hamilton et al. "New Method for Generating Deletions and Gene Replacements in Escherichia coli" Journal of Bacteriology, Sep. 1989, pp. 4617-4622, vol. 171, No. 9.
- Murphy G.L. et al. "Haemolytic activity of the Pasteurella haemolytica leukotoxin" Infection and Immunity, vol. 63, No. 8, Aug. 1995, pp. 3209-3212.
- Cruz W.T. et al. "Deletion analysis resolves cell-binding and lytic domains of the Pasteurella leukotoxin" Molecular Microbiology, vol. 4, No. 11, Nov. 1990, pp. 1933-1939.
- Petras S.F. et al. "Antigenic and virulence properties of Pasteurella haemolytica leukotoxin mutants" Infection and Immunity, vol. 63, No. 5, Mar. 1995, pp. 1033-1039.

ART-UNIT: 165

PRIMARY-EXAMINER: Graser; Jennifer E.

ABSTRACT:

Mutants of *P. haemolytica* provide excellent safety and efficacy when used as vaccines in ruminants, for example cattle, sheep, and goats, subject to pneumonic pasteurellosis. They can be administered by a variety of routes. Especially preferred is the use in animal feeds. The mutants are not reverting and contain no foreign DNA and no introduced antibiotic resistance genes.

3 Claims, 6 Drawing figures

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Dec 18, 2001

US-PAT-NO: 6331303

DOCUMENT-IDENTIFIER: US 6331303 B1

TITLE: LKTA deletion mutant of P. haemolytica

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Briggs; Robert E.	Boone	IA		
Tatum; Fred M.	Ames	IA		

US-CL-CURRENT: 424/255.1; 424/234.1, 435/252.3, 435/471, 435/69.1

CLAIMS:

We claim:

1. An isolated and purified P. haemolytica bacterium which:

a) expresses no biologically active leukotoxin,b) expresses a form of leukotoxin molecule which is a deletion mutant of about 66 kDa which lacks amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin; and

c) contains no foreign DNA.

2. The P. haemolytica bacterium of claim 1 wherein the bacterium is lktC.sup.30

3. P. haemolytica bacterium of claim 1 wherein the leukotoxin operon comprises no antibiotic resistance genes.

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L3: Entry 5 of 81

File: USPT

Dec 17, 2002

US-PAT-NO: 6495145

DOCUMENT-IDENTIFIER: US 6495145 B2

TITLE: LktA deletion mutant of P. haemolytica

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Briggs; Robert E.	Boone	IA		
Tatum; Fred M.	Ames	IA		

US-CL-CURRENT: 424/255.1; 424/234.1, 424/93.4, 426/2, 426/89, 435/455, 435/69.1

CLAIMS:

We claim:

1. A method of inducing immunity to pneumonic pasteurellosis in ruminants, comprising the step of: administering a P. haemolytica bacterium to a ruminant, wherein the P. haemolytica bacterium (a) expresses no biologically active leukotoxin, (b) expresses a form of leukotoxin molecule which is a deletion mutant of about 66 kDa which lacks amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin; and (c) contains no foreign DNA, whereby immunity is induced.
2. The method of claim 1 wherein the step of administering is via the oral route.
3. The method of claim 1 wherein the bacterium is top-dressed on the feed of the ruminant.
4. The method of claim 1 wherein the step of administering comprises injecting the bacterium subcutaneously.
5. The method of claim 1 wherein the step of administering comprises injecting the bacterium intradermally.
6. The method of claim 1 wherein the step of administering comprises injecting the bacterium intramuscularly.
7. The method of claim 1 wherein the step of administering is via the nose.
8. A feed for ruminants which comprises a P. haemolytica bacterium to a ruminant, wherein the P. haemolytica bacterium (a) expresses no biologically active leukotoxin, (b) expresses a form of leukotoxin molecule which is a deletion mutant of about 66 kDa which lacks amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin; and (c) contains no foreign DNA.
9. A vaccine for reducing morbidity in ruminants, comprising: a P. haemolytica bacterium (a) expresses no biologically active leukotoxin, (b) expresses a form of leukotoxin molecule which is a deletion mutant of about 66 kDa which lacks

amino acids 34 to 378 and which induces antibodies which specifically bind to and neutralize biologically active leukotoxin; and (c) contains no foreign DNA.

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File: USPT

Dec 17, 2002

US-PAT-NO: 6495145

DOCUMENT-IDENTIFIER: US 6495145 B2

TITLE: LktA deletion mutant of P. haemolytica

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Briggs; Robert E.	Boone	IA		
Tatum; Fred M.	Ames	IA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE	CODE
The United States of America as represented by the Secretary of Agriculture	Washington DC				06	
Biotechnology Research and Development Corporation	Peoria	IL			02	

APPL-NO: 09/ 982232 [PALM]

DATE FILED: October 19, 2001

PARENT-CASE:

This application is a division of co-pending Ser. No. 09/160,340 filed Sep. 25, 1998, now U.S. Pat. No. 6,331,303 which claims the benefit of co-pending provisional application Ser. No. 60/060,060, filed Sep. 25, 1997. Both applications are incorporated herein by reference.

INT-CL: [07] A61 K 39/102

US-CL-ISSUED: 424/255.1; 424/234.1, 424/93.4, 435/69.1, 435/455, 426/2, 426/89

US-CL-CURRENT: 424/255.1; 424/234.1, 424/93.4, 426/2, 426/89, 435/455, 435/69.1

FIELD-OF-SEARCH: 424/255.1, 424/234.1, 424/172.1, 424/252.3, 424/69.1, 424/93.4, 435/69.1, 435/320.1, 435/455, 435/243, 435/252.3, 536/23.7, 426/2, 426/89

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WO 97 16531	May 1997	WO	
WO 97/41823	November 1997	WO	

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George L. Murphy et al., "Hemolytic Activity of the Pasteurella haemolyticaLeukotoxin" Infection and Immunity, vol. 63, Aug. 1995, pp. 3209-3212.

Natalie D. Federova & Sarah K. Highlander "Generation of Targeted Nonpolar Gene Insertions and Operon Fusions in Pasteurella haemolytica and Creation of a Strain that Produces and Secretes Inactive Leukotoxin" Infection and Immunity, Jul. 1997, pp. 2593-2598.

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Link et al., "Methods for Generating Precise Deletions and Insertions in the Genome of Wild-Type Escherichia coli: Application to Open Reading Frame Characterization" Journal of Bacteriology, Oct. 1997, vol. 179, No. 20, pp. 628-6237.

Cotter and Miller "BvgAS-Mediated Signal Transduction: Analysis of Phase-Locked Regulatory Mutants of Bordetella bronchiseptica in a Rabbit Model", Infection and Immunity, Aug. 1994, vol. 62, No. 8, pp. 3381-3390.

Hamilton et al., "New Method for Generating Deletions and Gene Replacements in Escherichi coli", Journal of Bacteriology, Sep. 1989, vol. 171, No. 9, pp. 4617-4622.

Cruz W.T., et al., "Deletion analysis resolves cell-binding and lytic domains of the Pasteurella luktoxin" Molecular Microbioloty, vol. 4, No. 11, Nov. 1990, pp. 1933-1939.

Petras S.F. et al., "Antigenic and virulence properties of Pasteurella haemolytica leukotoxin mutants", Infection and Immunity, vol. 63, No. 5, Mar. 1995, pp. 1033-1039.

ART-UNIT: 1645 .

PRIMARY-EXAMINER: Wortman; Donna C.

ASSISTANT-EXAMINER: Zeman; Robert A.

ABSTRACT:

Mutants of *P. haemolytica* provide excellent safety and efficacy when used as vaccines in ruminants, for example cattle, sheep, and goats, subject to pneumonic pasteurellosis. They can be administered by a variety of routes. Especially preferred is the use in animal feeds. The mutants are not reverting and contain no foreign DNA and no introduced antibiotic resistance genes.

9 Claims, 6 Drawing figures